

Sarcoidosis and multiple myeloma: Concurrent presentation of an unusual association

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ABSTRACT

Literature on concurrent association of sarcoidosis with lymphoproliferative malignancies other than lymphoma e.g. multiple myeloma is meager. The rarity of the situation prompted us to report this patient who was a 51-year-old woman with a 2-years history of breathlessness, cough with expectoration, chest pain and backache. Initial evaluation revealed mild anemia, increased alkaline phosphatase with chest skiagram showing both lower zone non homogenous opacities with calcified hilar lymph nodes. CECT chest showed mediastinal with bilateral hilar lymphadenopathy, parenchymal fibrosis, traction bronchiectasis, ground glass opacities, septal and peribronchovascular thickening affecting mid and lower lung zones bilaterally. MRI Dorsolumbar spine was suggestive of marrow infiltrative disorder. EBUS FNA of intrathoracic nodes, EBB and TBLB confirmed sarcoidosis. PET CT revealed hyper metabolic activity in lung, multiple lymph nodes and lytic bone lesions. Serum protein electrophoresis and immunofixation revealed a monoclonal paraprotein, immunoglobulin IgG kappa type. Bone marrow biopsy revealed an increase in plasma cells (15%), but no granulomas. Diagnosis of Indolent or multiple myeloma with sarcoidosis was established. 12 cases of sarcoidosis and multiple myeloma have been reported in literature, and mostly preceding the onset of multiple myeloma by many years, in our case both were diagnosed concurrently.

KEY WORDS: Concurrent presentation, multiple myeloma, sarcoidosis

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INTRODUCTION

Association of sarcoidosis with lymphoproliferative malignancies is known and reported in literature.^[1] Epidemiological studies have suggested an increased incidence of lymphoma in patients with sarcoidosis on long-term follow-up, incidence estimated to being 11.5 times higher than expected in cohort of patients with Sarcoidosis alone and is referred as 'Sarcoid lymphoma syndrome'.^[1] Sarcoidosis has been also linked with acute myeloid leukemia (AML), where it may precede or develop years after quiescence of sarcoidosis.^[2] It has been suggested that chronicity of sarcoidosis and prolonged treatment with steroids and immunosuppressive drugs are

predisposing factors to development of malignancies. Multiple myeloma (MM), a hematoproliferative disease is rarely associated with sarcoidosis. However, the interval between diagnosis of the two entities is large (227 years) as reported in literature.^[3,4] We are reporting a case of sarcoidosis and multiple myeloma being diagnosed together concurrently.

CASE REPORT

A 51 year old woman was admitted with breathlessness, cough with scanty expectoration, diffuse central chest pain and low backache since 2 years. No significant past or family history.

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On examination, she had normal general physical examination with BP-126/70, pulse 76/min, SpO₂ on R.A.95%. Chest revealed bibasilar coarse crackles. Complete blood cell count, liver and kidney function tests were within normal limit. The patient's total serum protein level was 100 g/L (reference range, 60-80 g/L), serum IgE-38.4 (normal 0-167) and AEC210 (normal 40440). Chest skiagram showed bilateral lower zone haziness with few calcified lymph nodes at hila.

Montoux and interferogamma release assay (IGRA) negative, S.ACE186.3 (normal > or = 18 yrs: 852 U/L), S. Calcitriol 30 pg/ml (normal 19.654.3 pg/ml), S. Ca9.6 mg/dl (normal 8.511 mg/dl), 24 hour urinary Calcium 576 mg (normal 42353). Autoimmune profile including RA Factor, anti-CCP, ANCA, anti-dsDNA and ENA antibodies were negative. ANA weakly positive (1:100). Her lung function testing revealed FVC84% (2.130 lit), FEV₁72% (1.54 lit), FEV₁/FVC72.2% mild airflow obstruction with decreased diffusion capacity57% (12.36 ml/min/mmHg). On 6MWT she walked 330 m (56.1% of predicted) and oxygen saturation decreased significantly from 97% to 93%.

CECT chest and abdomen revealed evidence of mediastinal lymphadenopathy involving, right paratracheal, sub-carinal, prevascular and aorto-pulmonary and bilateral hilar lymph nodes with popcorn calcification in and few nodes. Lung parenchyma showed fibrosis and traction bronchiectasis along with septal thickening, peribronchial thickening and Ground Glass Opacities (GGO) more at bases [Figure 1a and b] In abdomen enlarged lymph nodes were seen in retrocrural, porta, retroperitoneum and peripancreatic areas.

Patient underwent fiberoptic bronchoscopy with transbronchial lung (TBLB) and endobronchial biopsy (EBB). Also, endobronchial ultrasound (EBUS)-guided aspiration done from mediastinal and hilar lymph nodes (4R, 7 and R10). Lymph node aspirates showed epithelioid cell granulomas with scanty necrosis, ZN stain for AFB and PAS was negative. Gene Xpert in both BAL and EBUS aspirate was negative for MTB, EBUS cell block showed noncaseating granuloma, TBLB revealed non-caseating granuloma [Figure 2]. These findings were consistent with diagnosis of sarcoidosis involving lungs and lymph nodes.

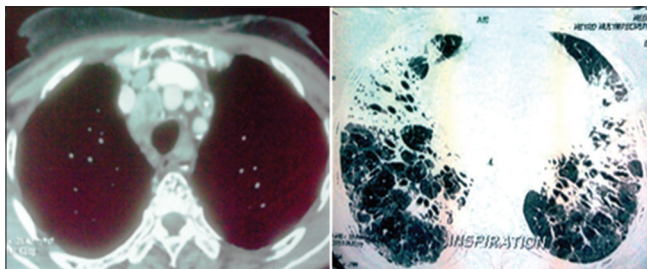


Figure 1: Mediastinal lymphadenopathy involving, right paratracheal, subcarinal, prevascular and aorto-pulmonary and bilateral hilar lymph nodes, lung parenchyma showed fibrosis and traction bronchiectasis along with septal thickening, peribronchial thickening and ground glass opacities (GGO)

Further, whole body PET-CT showed increased FDG uptake (SUVmax 7.0) was seen in both lungs predominantly in the lower lobes. Multiple areas of consolidation with air bronchograms, sub-pleural cystic changes and diffuse GGO's seen. Small irregular nodules with increased FDG uptake were seen in both lungs. Multiple FDG avid enhancing lymph nodes with calcification was seen bilaterally in supraclavicular/scaleneus (right > left, SUVma × 6.5), mediastinal, prevascular, bilateral paratracheal, aortopulmonary, subcarinal, bilateral parabronchial and hilar (SUVmax-5.9) areas. Abdominal lymph nodes showed increased FDG uptake (SUVmax-4.9) in retrocrural, paraaortic, gastrohepatic, periportal, and aorto-caval regions. Multiple lytic lesions with diffuse FDG uptake and trabeculae thickening involving axial skeleton cervicodorso-lumbar vertebrae, bilateral scapulae, ribs, sternum, sacrum, and pelvic bones [Figure 3a-e].

Serum protein electrophoresis revealed a monoclonal band, shown by immunofixation to be immunoglobulin (Ig) G k [Figure 4]. Quantification of serum immunoglobulin levels showed a high IgG level of 44.3 g/L (reference range, 716 g/L) and IgA 4.97 g/l (reference range, 0.462.87 g/L) and normal IgM (reference range, 0.57-2.37 g/L). Twenty-four-hour urine for calcium (576) showed hypercalciuria and negative for Bence-Jones protein. Beta 2 macroglobulin was 2896 pg/ml (normal 670-2143). Serum-free kappa light chain was 51.8 mg/L (normal 3.319.4), free Lambda (l.c) 27.9 mg/L (normal 5.71-26.3), and free kappa/lambda 1.86 (normal. 26-1.65). Urine-free kappa l.c-3.87 mg/L (normal 1.35-24.19), free lambda l.c5.52 (normal. 246.66), and free kappa/lambda 0.7 (2.0410.37).

Bone marrow aspiration show few binucleate forms and 15% plasma cells. Bone marrow biopsy showed no mass effect, 10% marrow cell replaced by plasma cells, mainly mature forms and immunohistochemistry for CD 138 was focally positive [Figure 5a-c] and diagnosis of indolent multiple myeloma were established. Later, X-ray of skull of the patient was done which showed multiple lytic lesions [Figure 6]. Hence, patient has been diagnosed as sarcoidosis with multiple myeloma together.

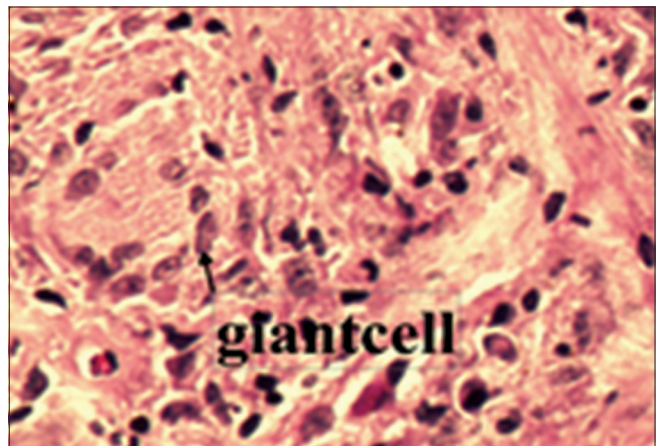


Figure 2: EBUS cell block shows noncaseating granuloma

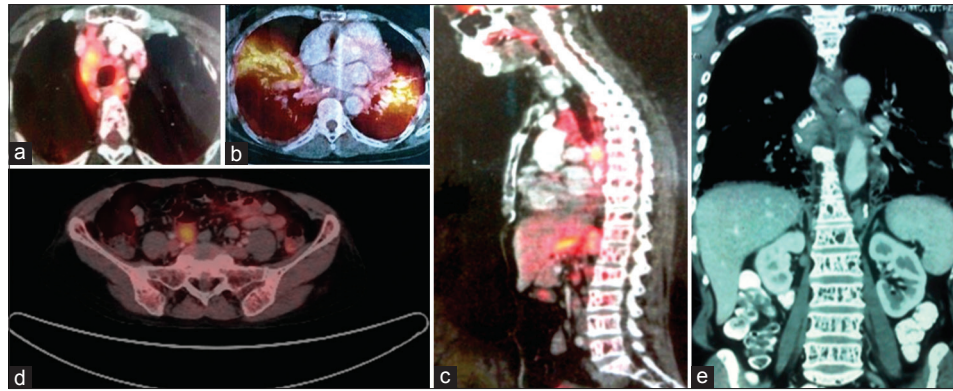


Figure 3: (a and b) Shows multiple FDG avid mediastinal and hilar lymphnodes and bilateral lower lobe consolidation and ground glass (c-e) Illustrates multiple FDG avid lytic lesions in axial skleton involving cervico-dorsal-lumbar vertebrae and pelvic bones correlating with bone window in sagittal cuts showing the same lytic lesions as mentioned

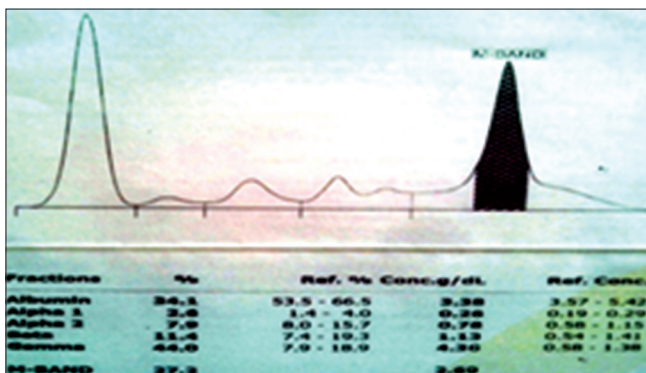


Figure 4: Serum protein electrophoresis revealed a monoclonal band, shown by immunofixation to be immunoglobulin (Ig) G k

Patient was started on prednisolone 40mg/day and simultaneously given chemotherapy with bortezomib, cyclophosphamide and responding well. She has received three cycles of chemotherapy and is presently stable on tapering doses of steroids (presently on prednisolone 20 mg/day).

DISCUSSION

The association of sarcoidosis with multiple myeloma in a patient being diagnosed concurrently is being reported here. In literature,^[3] 12 patients of sarcoidosis have been reported to have developed multiple myeloma, majority of multiple myeloma developing many years after sarcoidosis was diagnosed (median interval of 6 years), only two cases had both conditions being diagnosed simultaneously.^[5] In our case patient is a 51-year-old, which is significantly older than the general patient population with sarcoidosis.

Although epidemiologic study^[5,6] of 2544 patients of sarcoidosis have shown increased risk of lymphoproliferative malignancies and expected ratio of lymphoid malignancies in sarcoidosis is estimated to be 13.2, Hodgkin's disease was the most common. However, wide variety of T and B Cell neoplasms and leukemias have been reported to be associated with sarcoidosis. Sarcoid lymphoma syndrome

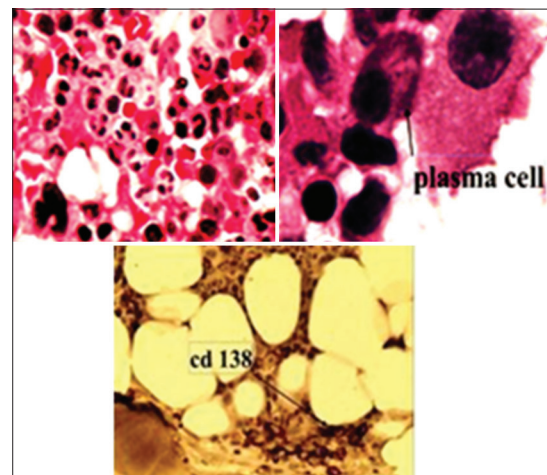


Figure 5: Bone marrow biopsy showed 10% marrow cell replaced by plasma cells, mainly mature forms and immunohistochemistry for CD 138 was focally positive

refers to the development of lymphoma at least 12 years after the diagnosis of sarcoidosis and other features being

1. Median age of onset of sarcoidosis in these patients tends to be 10 years above the unselected sarcoidosis patients, as in our patient.
2. B-cell type Hodgkin's lymphoma very common and T-cell lymphoma being highly uncommon.^[2,7]

The explanation for the relationship between sarcoidosis and multiple myeloma is unknown and controversial. Since, impaired immune system has been documented in sarcoidosis, it is possible that it predisposes them to develop malignancies. Cytogenetics studies^[8,9] in sarcoidosis have shown aneuploidy in the granuloma cells as well as peripheral blood lymphocytes, thereby creating genetic instability which may lead to development of hematological malignancies.

Also, it has been reported that untreated patients with pulmonary sarcoidosis have greater number of IgG and IgM secreting cells per 10^[3] lung lymphocytes vis a vis

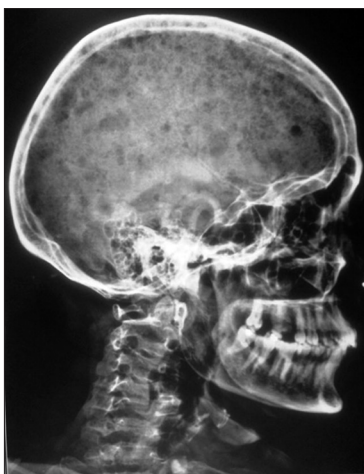


Figure 6: Lytic lesions on skull

normal population^[8] It was further demonstrated that purified T-lymphocytes from lungs of sarcoid patients when co-cultured with normal B cells, cell induction to secrete immunoglobulin secretory cells occurs, which clinically is seen as polyclonal hyper-gammaglobulinemia as seen in sarcoidosis.^[10] Extended half life of B cells and plasma cells along with overstimulation in sarcoidosis can lead to development of genetic mutation resulting in neoplastic transformation.^[9]

Our patient had indolent multiple myeloma and in other cases with sarcoidosis MGUS has been reported in 4/11 cases and it has been suggested that MGUS in sarcoidosis rapidly progress to multiple myeloma as compared to other patients of MGUS (16% develop multiple myeloma on follow-up for 30 years or more).^[11,12]

In our case, high FDG uptake was seen at many other sites other than clinico - radiologically suspected but it is difficult to distinguish the pattern of FDG uptake in sarcoidosis from metastatic malignancy. Fewer lesions on CT but asymptomatic numerous lesions on PET scan should raise the suspicion of sarcoidosis.^[13]

Abnormal lung uptake has been reported in 2/3rd of cases of sarcoidosis stages 2 and 3 indicating active disease. Our case showed intense uptake in both lungs at bases, though upper lobes is most commonly involved in sarcoidosis.^[1]

In summary we describe a patient with sarcoidosis and indolent multiple myeloma presenting concurrently at the time of diagnosis being rare and requiring high index of suspicion. At present this possible association is poorly characterized, as number of cases reports in literature are too small. Proof of a causal rather than a merely coincidental association between sarcoidosis and myeloma may be obtained only by prospective epidemiological studies but needs to be seriously considered keeping

in view that immunological dysfunction and genetic instability seen in sarcoidosis is predisposing factor in development of various malignancies particularly hematological in origin. Moreover, our patient presented with both the diseases at the same time, which makes it plausible that both conditions have same underlying process.^[3] Alternatively, a common primary immunological abnormality or etiological agent might lead to development of sarcoidosis and multiple myeloma together. Role of PET-CT scan in sarcoidosis is evolving and is anticipated to replace invasive procedures though needs more research to reach firmer correlation between uptake and cellular morphology. Our case suggests careful interpretation of FDG-PET in sarcoidosis as FDG avid lesions may be due to associated malignancies.

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Conflicts of interest

There are no conflicts of interest.

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